EXHIBIT S

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(54) **METHODS FOR TREATING CHRONIC OBSTRUCTIVE PULMONARY DISEASE**

(71) Applicant: **THERAVANCE BIOPHARMA R&D IP, LLC**, South San Francisco, CA (US)

(72) Inventors: **Christopher Noel Barnes**, South San Francisco, CA (US); **Glenn D. Crater**, South San Francisco, CA (US); **Edmund J. Moran**, South San Francisco, CA (US); **Srikanth Pendyala**, South San Francisco, CA (US)

(73) Assignee: **THERA VANCE BIOPHARMA R&D IP, LLC**, South San Francisco, CA (US)

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(63) Continuation of application No. 17/953,036, filed on Sep. 26, 2022, now abandoned, which is a continuation of application No. 16/555,216, filed on Aug. 29, 2019, now Pat. No. 11,484,531.

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(58) **Field of Classification Search**

None

See application file for complete search history.

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Primary Examiner — Leslie A. Royds Draper

(74) *Attorney, Agent, or Firm* — Sheppard Mullin Richter & Hampton LLP

(57) **ABSTRACT**

Methods for treating chronic obstructive pulmonary disease (COPD) in a patient are disclosed. In the methods, a patient having COPD is selected for treatment based on the patient's peak inspiratory flow rate (PIFR) and percent predicted force expiratory volume in one second (FEV_1); and a bronchodilator is administered to the selected patient using a nebulizer. Administration of a bronchodilator to patients having low PIFR and a percent predicted FEV_1 less than 50 percent using a nebulizer as the inhalation delivery device provides significantly greater improvements in trough FEV_1 and trough forced vital capacity (FVC) compared to administration of a bronchodilator to such patients using a dry powder inhaler.

14 Claims, No Drawings

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METHODS FOR TREATING CHRONIC OBSTRUCTIVE PULMONARY DISEASE

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation application of U.S. Ser. No. 17/953,036, filed on Sep. 26, 2022, which is a continuation application of U.S. Ser. No. 16/555,216, filed on Aug. 29, 2019, now U.S. Pat. No. 11,484,531, which claims the benefit of U.S. Provisional Application No. 62/724,805, filed on Aug. 30, 2018; the entire disclosures of which are incorporated herein by reference in their entireties.

BACKGROUND OF THE INVENTION

Field of the Invention

The present invention relates to methods for treating chronic obstructive pulmonary disease (COPD) in a patient. More specifically, in one of its aspects, the invention relates to methods for selecting a COPD patient for treatment based on the patient's peak inspiratory flow rate (PIFR) and percent predicted force expiratory volume in one second (FEV_1); and then administering a bronchodilator to the selected patient using a nebulizer.

State of the Art

COPD is a chronic inflammatory lung disease characterized by progressive persistent airflow obstruction. Bronchodilators, such as muscarinic receptor antagonists and β-adrenergic agonists, are commonly used to treat COPD. See, e.g., Vogelmeier, C. F. et al., *Am J Respir Crit Care Med,* 2017; 195(5), 557-582. Such bronchodilators are typically delivered to a patient in need of treatment using an inhalation delivery device, such as a dry powder inhaler, a metered dose inhaler or a nebulizer. See, e.g., Tashkin, D. P., *International Journal of COPD,* 2016; 11, 2585-2596. For many patients, any type of inhalation delivery device can be used to delivery an adequate dose of a bronchodilator. However, for COPD patients having a lower than normal inspiratory flow rate, nebulizers are sometimes recommended since these patients may be unable to generate a peak inspiratory flow rate sufficient for proper use of a dry powder inhaler. See, e.g., Mahler, D. A., *Ann Am Thorac Soc,* 2017; 14(7), 1103-1107; and Mahler, D. A. et al., *J Aerosol Med Pulm Drug Deliv,* 2014; 27(2), 103-109. Accordingly, use of a nebulizer for delivery of a bronchodilator has been suggested for COPD patients having low PIFR.

SUMMARY OF THE INVENTION

Surprisingly, it has now been discovered that low PIFR alone is not sufficient to predict which COPD patients will benefit from use of a nebulizer for delivery of a bronchodilator. In a clinical trial comparing the effects of bronchodilators delivered to COPD patients using either a nebulizer or a dry powder inhaler, it has unexpectedly been discovered that patients having both low PIFR and low percent predicted FEV_1 (<50%) achieved significantly greater improvements in trough FEV_1 and trough forced vital capacity (FVC) when a bronchodilator was administered using a nebulizer compared to a dry powder inhaler. In contrast, in patients having low PIFR and a percent predicted $FEV_1 \geq 50\%$, a significant difference in trough FEV_1 and FVC was not observed between patients using a nebulizer versus patients using a dry powder inhaler. Thus, it has now been discovered that COPD patients having low PIFR and a percent predicted $FEV_1 < 50\%$ will gain additional benefit from a bronchodilator if the bronchodilator is delivered to such patients using a nebulizer instead of a dry powder inhaler. This unexpected discovery can be used to select COPD patients for treatment with a bronchodilator using a nebulizer thereby improving the therapeutic outcome for such patients.

Accordingly, in one aspect, the present invention relates to a method for treating chronic obstructive pulmonary disease in a patient comprising: (a) selecting a patient having a peak inspiratory flow rate (PIFR) less than about 60 L/min and a percent predicted force expiratory volume in one second (FEV_1) less than about 50 percent; and (b) administering a bronchodilator to the selected patient using a nebulizer.

In another aspect, the present invention relates to a method comprising: (a) determining the peak inspiratory flow rate (PIFR) of the patient; (b) determining the percent predicted force expiratory volume in one second (FEV_1) of the patient; (c) selecting the patient for treatment with a bronchodilator administered using a nebulizer if the patient has a PIFR less than about 60 L/min and a percent predicted FEV_1 less than about 50 percent; and (d) administering the bronchodilator to the selected patient using the nebulizer.

Unless otherwise indicated, the following separate and distinct embodiments are applicable for each aspect of the invention described herein.

In one embodiment of the methods of this invention, the patient has a PIFR less than about 50 L/min; including less than about 40 L/min; such as less than about 30 L/min. In one embodiment, the patient has a percent predicted FEV_1 less than 40 percent; including less than 30 percent. In one embodiment, the patient has a PIFR in the range of about 20 L/min to less than about 60 L/min and a percent predicted FEV_1 in the range of from about 20 percent to less than about 50 percent.

In one embodiment, the bronchodilator employed in the methods of this invention is a muscarinic antagonist; a β-adrenergic receptor agonist; a muscarinic antagonist-β-adrenergic receptor agonist (MABA); or a combination of a muscarinic antagonist and a β-adrenergic receptor agonist.

In one embodiment, the bronchodilator is a muscarinic antagonist. In another embodiment, the bronchodilator is a muscarinic antagonist selected from aclidinium, glycopyrronium, ipratropium, revefenacin, tiotropium and umeclidinium; or a pharmaceutically acceptable salt thereof. In a particular embodiment, the muscarinic antagonist is revefenacin or a pharmaceutically acceptable salt thereof.

In one embodiment, the bronchodilator is a β-adrenergic receptor agonist. In another embodiment, the bronchodilator is a β-adrenergic receptor agonist is selected from albuterol, arformoterol, formoterol, indacaterol, levalbuterol, metaproterenol, salmeterol, terbutaline, and vilanterol; or a pharmaceutically acceptable salt thereof.

In one embodiment, the bronchodilator is a muscarinic antagonist-β-adrenergic receptor agonist (MABA). In a particular embodiment, the bronchodilator is batefenterol or a pharmaceutically acceptable salt thereof.

In one embodiment, the bronchodilator is a combination of a muscarinic antagonist and a β-adrenergic receptor agonist.

In another aspect, the present invention relates to a method for treating chronic obstructive pulmonary disease in a patient, the method comprising: (a) selecting a patient

having a peak inspiratory flow rate (PIFR) less than about 60 L/min and a percent predicted force expiratory volume in one second (FEV_1) less than about 50 percent; and (b) administering a pharmaceutical composition comprising an aqueous solution of revefenacin or a pharmaceutically acceptable salt thereof to the selected patient using a nebulizer.

Unless otherwise indicated, the following separate and distinct embodiments are applicable for each aspect of the invention described herein.

In one embodiment, the pharmaceutical composition has a pH in the range of about 4.5 to about 5.5. In another embodiment, the pharmaceutical composition has a pH of about 4.8 to about 5.2; including about 5.

In one embodiment, the pharmaceutical composition is isotonic.

In one embodiment, the pharmaceutical composition further comprises a tonicity agent and a buffer. In another embodiment, the pharmaceutical composition further comprises sodium chloride, citric acid and sodium citrate.

In one embodiment, the pharmaceutical composition is sterile, isotonic and has a pH of about 5.

In one embodiment, the pharmaceutical composition comprises about 20 μg/mL to about 60 μg/mL of revefenacin or a pharmaceutically acceptable salt thereof. In another embodiment, the pharmaceutical composition comprises about 88 μg/3 mL of revefenacin or a pharmaceutically acceptable salt thereof. In another embodiment, the pharmaceutical composition comprises about 175 μg/3 mL of revefenacin or a pharmaceutically acceptable salt thereof.

In one embodiment, the pharmaceutical composition is administered using a jet nebulizer.

In another aspect, the present invention relates to a method for selecting a patient having COPD for treatment with a bronchodilator administered using a nebulizer, the method comprising (a) determining the peak inspiratory flow rate (PIFR) of the patient; (b) determining the percent predicted force expiratory volume in one second (FEV_1) of the patient; and (c) selecting the patient for treatment with a bronchodilator administered using a nebulizer if the patient has a PIFR less than about 60 L/min and a percent predicted FEV_1 less than about 50 percent.

In another aspect, the present invention relates to a method for selecting a nebulizer as the inhalation delivery device used to administer a bronchodilator to a patient having COPD, the method comprising (a) determining the peak inspiratory flow rate (PIFR) of the patient; (b) determining the percent predicted force expiratory volume in one second (FEV_1) of the patient; and (c) selecting a nebulizer to administer a bronchodilator to the patient if the patient has a PIFR less than about 60 L/min and a percent predicted FEV_1 less than about 50 percent.

Other aspects and embodiments of this invention are disclosed herein.

DETAILED DESCRIPTION OF THE INVENTION

In its various aspects and embodiments, the present invention provides methods relating to the treatment of COPD in a patient based on the patient's peak inspiratory flow rate (PIFR) and percent predicted force expiratory volume in one second (FEV_1).

Definitions

When describing the present invention, the following terms have the following meanings unless otherwise indicated.

The singular terms "a," "an" and "the" include the corresponding plural terms unless the context of use clearly dictates otherwise.

The term "about" means ±10 percent of the specified value.

The term "low peak inspiratory flow rate" or "low PIFR" means a peak inspiratory flow rate less than about 60 L/min. Low peak inspiratory flow rate is also referred to as suboptimal peak inspiratory flow rate.

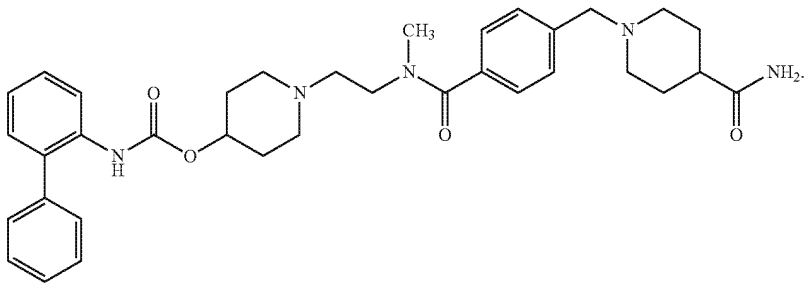
The term "peak inspiratory flow rate" or "PIFR" means the maximal flow rate achievable from a forced inspiration with an open glottis starting from a position of full expiration, typically expressed in liters/minute.

The term "peak inspiratory flow rate less than about 60 L/min" means a peak inspiratory flow rate less than about 60 L/min against a resistance of about 23 $\sqrt{kPa}\cdot L^{-1}\cdot min\cdot 10^{-3}$ (e.g., against the simulated resistance of a DISKUS® device) or an equivalent thereof. Similarly, other terms such as "peak inspiratory flow rate less than about 50 L/min" and the like mean a peak inspiratory flow rate determined against a resistance of about 23 $\sqrt{kPa}\cdot L^{-1}\cdot min\cdot 10^{-3}$ (e.g., against the simulated resistance of a DISKUS® device) or an equivalent thereof.

The term "pharmaceutically-acceptable" means acceptable for administration to a patient (e.g., having acceptable safety for the specified usage).

The term "pharmaceutically-acceptable salt" means a salt prepared from an acid and a base (including zwitterions) that is acceptable for administration to a patient (e.g., a salt having acceptable safety for a given dosage regime).

The term "revefenacin" means 1-(2-{4-[(4-carbamoylpiperidin-1-yl)methyl]-N-methylbenzamido}ethyl) piperidin-4-yl N-([1,1'-biphenyl]-2-yl)carbamate (alternatively known as biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester) having chemical structure:



As used herein, the term "revefenacin" is intended to include revefenacin (free base) and pharmaceutically acceptable salts of revefenacin unless otherwise indicated.

The term "therapeutically effective amount" means an amount sufficient to effect treatment when administered to a patient in need of treatment, e.g., the amount needed to obtain the desired therapeutic effect.

The term "treating" or "treatment" means ameliorating or suppressing the medical condition or disorder being treated; or alleviating the symptoms of the medical condition or disorder.

All other terms used herein are intended to have their ordinary meaning as understood by persons having ordinary skill in the art to which they pertain.

Bronchodilators

Any suitable bronchodilator can be used in the present invention. Representative examples of types or classes of bronchodilators suitable for use in the present invention include muscarinic antagonists; β-adrenergic receptor agonists; muscarinic antagonist-β-adrenergic receptor agonists (MABAs); and combinations of a muscarinic antagonist and a β-adrenergic receptor agonist.

In one embodiment, the bronchodilator is a muscarinic antagonist. The muscarinic antagonist can be a short-acting muscarinic antagonist (SAMA) or a long-acting muscarinic antagonists (LAMA). Representative examples of muscarinic antagonists include, but are not limited to, aclidinium, glycopyrronium, ipratropium, revefenacin, tiotropium, umeclidinium, and the like; and pharmaceutically acceptable salts thereof. Particular examples of pharmaceutically acceptable salts of muscarinic antagonists include aclidinium bromide, glycopyrronium bromide, ipratropium bromide, tiotropium bromide, umeclidinium bromide, and the like. In a particular embodiment, the muscarinic antagonist is revefenacin or a pharmaceutically acceptable salt thereof. In another particular embodiment, the muscarinic antagonist is glycopyrronium or a pharmaceutically acceptable salt thereof; including glycopyrronium bromide.

The muscarinic antagonists employed in the present invention are commercially available or can be prepared by well-known procedures. For example, methods for preparing muscarinic antagonists are described in U.S. Pat. Nos. 6,777,423; 7,288,657; 7,488,827; 7,498,440; 8,754,225; and the like.

In another embodiment, the bronchodilator is a β-adrenergic receptor agonist. The β-adrenergic receptor agonist can be a short-acting β-adrenergic receptor agonist (SABA) or a long-acting β-adrenergic receptor agonist (LABA). Representative examples of β-adrenergic receptor agonists include, but are not limited to, albuterol, arformoterol, formoterol, indacaterol, levalbuterol, metaproterenol, olodaterol, salmeterol, terbutaline, vilanterol, and the like; or a pharmaceutically acceptable salt thereof. Particular examples of pharmaceutically acceptable salts of β-adrenergic receptor agonists include albuterol sulfate, arformoterol tartrate, formoterol fumarate, indacaterol maleate, levalbuterol hydrochloride, metaproterenol sulfate, olodaterol hydrochloride, salmeterol xinafoate, terbutaline sulfate, vilanterol trifenatate, and the like. In a particular embodiment, the β-adrenergic receptor agonist is selected from arformoterol, formoterol, indacaterol, olodaterol, salmeterol, vilanterol; or a pharmaceutically acceptable salt thereof.

The β-adrenergic receptor agonists employed in the present invention are commercially available or can be prepared by well-known procedures. For example, methods for preparing β-adrenergic receptor agonists are described in U.S. Pat. Nos. 6,878,721; 7,439,393; 7,727,984; RE44,874; and the like.

In another embodiment, the bronchodilator is a muscarinic antagonist-β-adrenergic receptor agonist (MABA). In a particular embodiment, the bronchodilator is batefenterol and the like; or a pharmaceutically acceptable salt thereof. Particular examples of pharmaceutically acceptable salts of MABAs include batefenterol succinate and the like.

The MABAs employed in the present invention are commercially available or can be prepared by well-known procedures. For example, methods for preparing MABAs are described in U.S. Pat. Nos. 7,345,175; 7,960,551; 8,101,766; 8,138,345; and the like.

In one embodiment, the bronchodilator is a combination of a muscarinic antagonist and a β-adrenergic receptor agonist. Representative combinations include, but are not limited to, albuterol and ipratropium; tiotropium and olodaterol; revefenacin and formoterol; umeclidinium and vilanterol; and the like; and pharmaceutically acceptable salts thereof.

Pharmaceutical Compositions

Any pharmaceutical composition suitable for use in a nebulizer can be employed in the present invention. Typically, such pharmaceutical compositions comprise a bronchodilator and a pharmaceutically acceptable carrier. Representative pharmaceutically acceptable carriers include, but are not limited to, water and water/ethanol mixtures. The bronchodilator may be present in the pharmaceutically acceptable carrier as a solution or a suspension. Such pharmaceutical compositions may also optionally contain one or more additional excipients. See, e.g., Thorat, *IJPSR*, 2016; 1(5): 30-35.

Representative types of excipients that may be employed in the pharmaceutical composition include, by way of example, buffers, preservatives, co-solvents, suspending agents, surfactants, tonicity adjusting agents, humectants, cation chelating agents, and the like. Examples of buffers (used to buffer the pH of the formulation) include, but are not limited to, citric acid, sodium citrate, sodium phosphate and the like. Examples of preservatives (used, e.g., to prevent microbial growth in the formulation) include, but are not limited to, benzalkonium chloride, ethanol, propylene glycol, benzyl alcohol, chlorobutanol, methyl paraben and the like. Examples of co-solvents (used to improve solubility) include, but are not limited to, ethanol, PEG 400, propylene glycol and the like. Examples of suspending agents (used to increase the viscosity and suspendability of a suspension) include, but are not limited to, carboxymethyl cellulose, sodium carboxymethyl cellulose, and the like. Examples of surfactants (used to increase the suspendability and stability of a suspension) include, but are not limited to, polysorbate 20, polysorbate 80 and the like. Examples of tonicity adjusting agents (used to adjust the tonicity of the formulation) include, but are not limited to, sodium chloride, dextrose and the like. Examples of humectants (used to maintain moisture in the formulation) include, but are not limited to, glycerin and the like. Examples of cation chelating agents (used to form chelates with ions present in the formulation and to increase stability) include, but are not limited to disodium EDTA and the like. Additionally, pH adjusting agents may be used to adjust the pH of the formulation. Examples of pH adjusting agents include, but art not limited to, sodium hydroxide, hydrochloric acid, sulfuric acid and the like.

In general, when an excipient is employed in the pharmaceutical composition, the excipient will be used in an

amount sufficient to perform its desired function. Such an amount is either known in the art or is readily determined by routine experimentation. For example, the amount of tonicity agent present in the pharmaceutical composition typically ranges from about 0.1 to about 5 wt. % based on the total weight of the composition; including about 0.5 to about 3 wt. %; such as about 1 to about 2 wt. %. The amount of buffer or buffering agent present in the pharmaceutical composition typically ranges from about 0.1 to about 5 wt. % based on the total weight of the composition; including about 0.5 to about 3 wt. %; such as about 1 to about 2 wt. %.

In one embodiment, the pharmaceutically composition comprises a bronchodilator and an aqueous carrier. In one embodiment, this pharmaceutical composition further comprises one or more excipients. In another embodiment, this pharmaceutical composition further comprises a buffer and a tonicity agent. In a particular embodiment, the pharmaceutical composition further comprises sodium citrate, citric acid and sodium chloride.

In one embodiment, the pharmaceutical composition is sterile.

In one embodiment, the pharmaceutical composition is isotonic.

In one embodiment, the pharmaceutical composition has a pH of about 4 to about 6. In another embodiment, the pharmaceutical composition has a pH of about 4.5 to about 5.5. In another embodiment, the pharmaceutical composition has a pH of about 4.8 to about 5.2; including about 5.

In one embodiment, the pharmaceutical composition is sterile, isotonic and has a pH of about 4.8 to about 5.2; including about 5.

A representative pharmaceutical composition for use in a nebulizer comprises an isotonic aqueous solution comprising from about 0.05 μg/mL to about 10 mg/mL of a bronchodilator; including about 10 μg/mL to about 100 μg/mL of the bronchodilator; or about 30 μg/mL to about 60 μg/mL of the bronchodilator. In one embodiment, this solution contains a tonicity agent comprising sodium chloride. In one embodiment, this solution contains a buffer comprising citric acid and sodium citrate. In one embodiment, this solution has a pH of about 4 to about 6; including about 4.8 to about 5.2; including about 5.

Typically, the pharmaceutical composition is prepared by dissolving the bronchodilator and any optional excipients in the pharmaceutically acceptable carrier and adjusting the pH of the composition to the desired pH using a pH adjusting agent. In one embodiment, the excipients are first dissolved in the carrier and the pH is adjusted, and then the bronchodilator is dissolved in the resulting composition. Alternatively, if the bronchodilator is not soluble in the carrier, the bronchodilator can be micronized and combined with a suitable composition to form a suspension of micronized particles.

Nebulizers

Any suitable nebulizer can be using in this invention including, by way of example, jet nebulizers, ultrasonic nebulizers and vibrating mesh nebulizers. See, e.g., Ari, *Eurasian J Pulmonol,* 2014; 16: 1-7 and Thorat, *IJPSR,* 2016; 1(5): 30-35. Jet nebulizers include, for example, (a) jet nebulizers with a corrugated tube; (b) jet nebulizers with a collection bag; (c) breath-enhanced jet nebulizers; and (d) breath-actuated jet nebulizers. Representative examples of jet nebulizers include, but are not limited to, the AKITA® JET nebulizer (Vectura, Chippenham, UK); the AEROECLIPSE® (Trudell Medical International, London, Ontario, Canada); the CIRCULAIRE® (Westmed INC, Tucson, AZ, USA); the InnoSpire Mini Compressor nebulizer (Philips Healthcare, Andover, MA, USA); the NEBU TECH® (Salter Labs, Arvin, CA, USA); the PARI LC PLUS®, and the PARI LC® Sprint (PARI, Starnberg, Germany); the TREK® S jet nebulizer (PARI, Midlothian, VA, USA); and the like. Representative examples of ultrasonic nebulizers include, but are not limited to, MICRO AIR® Electronic (Omron Healthcare, Bannockburn, IL, USA); MINIBREEZE™ Ultrasonic (Mabis, Waukegan, IL, USA); the FLPY™ (Convexity Scientific, Westport, CT, USA); and the like. Representative examples of vibrating mesh nebulizers include, but are not limited to, AEROGEN® Solo (Aerogen, Chicago, IL, USA); EFLOW® (PARI, Starnberg, Germany); and the like. Such nebulizers are used according to the manufacturer's instructions.

Determination of PIFR and Percent Predicted FEV_1

Peak inspiratory flow rate (PIFR) and percent predicted force expiratory volume in one second less (FEV_1) are determined using standard procedures known in the art. See, e.g., Sharma et al., *Chronic Obstr Pulm Dis.* 2017; 4(3): 217-224.

For example, PIFR can be determined using a handheld peak inspiratory flow meter, such as the IN-CHECK® DIAL device (Clement Clarke Ltd. Harlow, UK or Alliance Tech Medical, Granbury, TX, USA). See, e.g., Van der Palen, *Respr Med* 2003; 97: 285-289. When using the IN-CHECK® DIAL device, the resistance of the device is set to simulate the resistance of a dry powder inhaler (DPI) device, such as the DISKUS® device. The resistance of the DISKUS® device has been calculated to be 22.96 $\sqrt{kPa}\cdot L^{-1}\cdot min\cdot 10^{-3}$ or about 23 $\sqrt{kPa}\cdot L^{-1}\cdot min\cdot 10^{-3}$ (see, e.g., Kondo et al., *Jpn J Pharm Health Care Sci,* 40(6), 344-351 (2014)). Accordingly, in a particular embodiment, PIFR is determined against a resistance of about 23 $\sqrt{kPa}\cdot L^{-1}\cdot min\cdot 10^{-3}$. In another particular embodiment, PIFR is determined using the IN-CHECK® DIAL device with the resistance set to the DISKUS® setting or set to Med Low (ACCUHALER® or DISKUS®). When used according to the manufacturer's instructions, PIFR (L/min) is read from the scale on the IN-CHECK® DIAL device. Alternatively, PIFR can be determined using baseline spirometric parameters as described, e.g., in Seheult et al. *SpringerPlus* 2014, 3:496.

Those skilled in the art will appreciate that the PIFR determined for a given patient will vary depending on the method and the resistance used to measure PIFR and that, for purposes of the present invention, low PIFR includes equivalents of PIFR less than about 60 L/min when measured against a resistance of about 23 $\sqrt{kPa}\cdot L^{-1}\cdot min\cdot 10^{-3}$.

Percent predicted FEV_1 is determined by comparing measured FEV_1 for a patient with predicted FEV_1 for that patient based on the patient's age, race, height and gender (i.e., measured FEV_1/predicted $FEV_1 \times 100$=percent predicted FEV_1). FEV_1 is measured using a standard spirometry test or pulmonary function test which involves forcefully breathing out into a mouthpiece connected to a spirometer. See, e.g., Miller et al., *Eur Respir J,* 2005; 26: 319-338. Predicted FEV_1 is calculated based on age, race, height and gender using well-known procedures. For example, the Centers for Disease Control and Prevention provide an online calculator that can be used to determine predicted FEV_1 (www.cdc.gov/niosh/topics/spirometry/refcalculator.html).

Selection of a Patient or a Nebulizer for Treatment

In one aspect of the present invention, a patient having COPD is selected for treatment with a bronchodilator administered using a nebulizer if the patient has a PIFR less than about 60 L/min and a percent predicted FEV_1 less than

about 50 percent. In another aspect of the invention, a nebulizer is selected as the inhalation delivery device used to administer a bronchodilator to a patient having COPD if the patient has a PIFR less than about 60 L/min and a percent predicted FEV_1 less than about 50 percent.

In one embodiment, PIFR is less than about 50 L/min. In another embodiment, PIFR is less than about 40 L/min. In another embodiment, PIFR is less than about 30 L/min. In one embodiment, percent predicted FEV_1 is less than about 40 percent. In another embodiment, percent predicted FEV_1 is less than about 30 percent. Particular embodiments include those where PIFR (L/min) and percent predicted FEV_1 (%) are about: <60 and <50; <50 and <50; <40 and <50; <60 and <40; <50 and <40; <40 and <40; <60 and <30; <50 and <30; <40 and <30, respectively. In another particular embodiment, the patient has a PIFR in the range of about 20 L/min to less than about 60 L/min and a percent predicted FEV_1 in the range of from about 20 percent to less than about 50 percent.

In one embodiment of the method, PIFR and percent predicted FEV_1 have been determined previously and the patient is selected based on such predetermined values. Alternatively, in another embodiment, the method includes the steps of determining PIFR and FEV_1 for a patient and then selecting the patient for treatment with a bronchodilator administered using a nebulizer inhaler if the patient has a PIFR less than about 60 L/min and a percent predicted FEV_1 less than about 50 percent.

Administration of the Bronchodilator to the Patient

Once a patient has been selected, the bronchodilator is administered to the selected patient using a nebulizer. The dose of the bronchodilator administered to the patient is typically determined by a physician based on the severity of the patient's condition and other factors, including the recommended or approved dose for the bronchodilator. Representative doses include, but are not limited to, about 5 μg to about 500 μg of the bronchodilator once or twice per day depending the bronchodilator. In one embodiment, the bronchodilator is revefenacin administered at a dose of about 88 μg once per day. In another embodiment, the bronchodilator is revefenacin administered at a dose of about 175 μg once per day. Once selected, the dose is administered using a nebulizer according to the manufacturer's instructions.

EXAMPLES

The following examples are provided to illustrate various representative embodiments and aspects of this invention and are not intended to limit the scope of this invention unless specifically indicated.

Example 1

Clinical Study Comparing a Bronchodilator Administered with Nebulizer Inhaler to a Bronchodilator Administered with Dry Powder Inhaler

A 28-day, randomized, double-blind, double-dummy, parallel-group study was conducted to compare once-daily revefenacin (175 μg of revefenacin in 3 mL of an isotonic, sterile aqueous solution containing sodium chloride, citric acid, sodium citrate, and water for injection at pH 5.0) delivered using a nebulizer (Trek S jet nebulizer (PARI, Midlothian, VA, USA) with once-daily tiotropium (18 μg/day) delivered using a dry powder inhaler (Spiriva HandiHaler, Boebringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT, USA) on lung function in subjects with chronic obstructive pulmonary disease and a low peak inspiratory flow rate. Subjects with moderate to very severe COPD were allowed to use concurrent respiratory therapy with the exception of other inhaled anticholinergics. The primary endpoint of the study was the change from baseline in trough forced expiratory volume in one second (FEV_1) after the 28^{th} dose. Secondary endpoints included the change from baseline in peak FEV_1, trough forced vital capacity (FVC), peak FVC and trough inspiratory capacity (IC) as well as the safety and tolerability of revefenacin 175 μg. Inclusion criteria were: age≥40 years; a smoking history≥10 pack years; a diagnosis of COPD (post-bronchodilator FEV_1≤80% predicted and FEV/FVC≤70%); peak inspiratory flow rate (PIFR)<60 L/min as measured by IN-CHECK® DIAL device with resistance set to DISKUS® at screening.

The baseline characteristics of the patients included in the study are shown in Table 1. The tiotropium and revefenacin groups were well-balanced on age, sex, race, body mass index (BMI), smoking history, use of inhaled corticosteroids/long-acting beta agonists (ICS/LABA), rating in modified Medical Research Council (mMRC) dyspnea scale, and their spirometry measurements.

TABLE 1

Key Demographics and Baseline Clinical Characteristics

	Tiotropium (N = 104)	Revefenacin (N = 102)
Age, mean (SD)	65.1 (8.36)	65.1 (7.94)
Sex (male), n (%)	64 (61.5%)	60 (58.8%)
Race (white), n (%)	95 (91.3%)	90 (88.2%)
BMI, mean (SD)	27.3 (6.50)	27.6 (6.85)
Current smoker (yes), n (%)	50 (48.1%)	46 (45.1%)
Concurrent ICS/LABA use (yes), n (%)	57 (54.8%)	54 (52.9%)
Post-ipratropium percent predicted FEV_1, mean (SD)	37.1 (15.06)	36.6 (16.17)
Post-ipratropium FEV_1 to FVC (ratio), mean (SD)	0.43 (0.109)	0.42 (0.114)
Baseline FEV_1 (in mL), mean (SD)	0.93 (0.417)	0.90 (0.493)
Baseline FVC, mean (SD)	2.22 (0.696)	2.15 (0.739)
Baseline IC, mean (SD)	1.71 (0.600)	1.65 (0.568)
Baseline PIFR (L/min), mean (SD)	45.4 (11.21)	45.3 (11.91)
Proportion of subjects with Baseline mMRC ≥2, n (%)	78 (75.0%)	76 (74.5%)
Proportion of subjects with ≤1 exacerbations in prior year, n (%)	93 (89.4%)	94 (92.2%)

In this study, revefenacin (REV) (administered using a nebulizer) or tiotropium (TIC)) (administered using a dry powder inhaler) was dosed once-daily for 28 days, Peak inspiratory flow rates (best of three) were determined at screening, randomization and end of study using the IN-CHECK® DIAL device with the resistance set to a resistance equal or similar to the resistance associated with the DISKUS® device. FEV_1, FVC and IC were measured at baseline and/or peak on day 1 and on day 29. Safety was assessed via the collection of adverse events.

In the intention-to-treat (ITT) population, there were trends favoring revefenacin administered using a nebulizer over tiotropium administered using a dry powder inhaler for trough FEV_1 and FVC, but such trends did not meet statistical significance nor clinical relevance. However, in subjects with more severe airflow limitation (FEV_1<50% predicted), there were statistically significant and clinically relevant greater improvements in both trough FEV_1 and FVC for revefenacin administered using a nebulizer compared to tiotropium administered using a dry powder inhaler.

No differences in trough IC were noted. The data for trough FEV_1, FVC and IC are shown in Tables 2, 3 and 4, respectively.

TABLE 2

Trough Forced Expiratory Volume in One Second (Trough FEV_1) (All Subjects PIFR <60 L/min)

	ITT Population		% Predicted FEV_1 <50% Subpopulation	
Trough FEV_1	TIO 18 µg (N = 104)	REV 175 µg (N = 102)	TIO 18 µg (N = 81)	REV 175 µg (N = 80)
LS Mean (SE)	47.3 (19.06)	63.0 (20.17)	27.5 (19.53)	74.8 (20.85)
LS Difference (SE)		15.7 (22.35)		47.3 (21.76)
Nominal P-Value		0.4811		0.0302

The data in Table 2 shows that a statistically significant difference in trough FEV_1 was observed for subjects treated with revefenacin (REV) administered using a nebulizer compared to subjects treated with tiotropium (TIO) administered using a dry powder inhaler if the subjects had both low PIFR (<60 L/min) and a percent predicted FEV_1<50%. Surprisingly, a statistically significant difference in trough FEV_1 was not observed for all subjects (ITT population) even though all subjects had low PIFR and the literature suggests that such a difference should be observed.

TABLE 3

Trough Forced Vital Capacity (Trough FVC) (All Subjects PIFR <60 L/min)

	ITT Population		% Predicted FEV_1 <50% Subpopulation	
Trough FVC	TIO 18 µg (N = 104)	REV 175 µg (N = 102)	TIO 18 µg (N = 81)	REV 175 µg (N = 80)
LS Mean (SE)	55.8 (36.62)	125.4 (38.75)	46.7 (43.56)	146.5 (46.69)
LS Difference (SE)		69.6 (42.90)		99.9 (48.75)
Nominal P-Value		0.1040		0.0407

The data in Table 3 shows that a statistically significant difference in trough FVC was observed for subjects treated with revefenacin (REV) administered using a nebulizer compared to subjects treated with tiotropium (TIO) administered using a dry powder inhaler if the subjects had both low PIFR (<60 L/min) and a percent predicted FEV_1<50%. Surprisingly, a statistically significant difference in trough FVC was not observed for all subjects (ITT population) even though all subjects had low PIFR.

TABLE 4

Trough Inspiratory Capacity (Trough IC) (All Subjects PIFR <60 L/min)

	ITT Population		% Predicted FEV_1 <50% Subpopulation	
Trough IC	TIO 18 µg (N = 104)	REV 175 µg (N = 102)	TIO 18 µg (N = 81)	REV 175 µg (N = 80)
LS Mean (SE)	84.1 (40.02)	71.4 (42.33)	76.0 (40.40)	89.7 (42.85)
LS Difference (SE)		−12.7 (47.38)		13.7 (45.43)
Nominal P-Value		0.7871		0.7606

The data in Table 4 shows that a statistically significant difference in trough IC was not observed for subjects treated with revefenacin (REV) administered using a nebulizer compared to subjects treated with tiotropium (TIO) administered using a dry powder inhaler in either all subjects (ITT population) or in a subject subpopulation having both low PIFR (<60 L/min) and a percent predicted FEV_1<50%.

While the present invention has been described with reference to specific aspects or embodiments thereof, it will be understood by those of ordinary skilled in the art that various changes can be made or equivalents can be substituted without departing from the true spirit and scope of the invention. Additionally, to the extent permitted by applicable patent statutes and regulations, all publications, patents and patent applications cited herein are hereby incorporated by reference in their entirety to the same extent as if each document had been individually incorporated by reference herein.

What is claimed is:

1. A method for treating chronic obstructive pulmonary disease (COPD) in a patient with severe to very severe COPD, the method comprising:

(a) selecting a patient having a percent predicted forced expiratory volume in one second less than 50 percent; and

(b) administering a pharmaceutical composition comprising an aqueous solution of revefenacin or a pharmaceutically acceptable salt thereof to the selected patient using a nebulizer;

wherein the patient has a low peak inspiratory flow rate.

2. The method of claim **1**, wherein the low peak inspiratory flow rate is less than about 50 L/min.

3. The method of claim **1**, wherein the patient has a percent predicted forced expiratory volume in one second less than about 40 percent.

4. The method of claim **1**, wherein the patient has a percent predicted forced expiratory volume in one second less than about 30 percent.

5. The method of claim **1**, wherein the patient has very severe COPD.

6. The method of claim **1**, wherein the patient has a peak inspiratory flow rate in the range of about 20 L/min to less than about 60 L/min and a percent predicted forced a percent predicted forced expiratory volume in one second in the range of from about 20 percent to less than 50 percent.

7. The method of claim **1**, wherein the pharmaceutical composition comprises about 175 μg/3 mL of revefenacin or a pharmaceutically acceptable salt thereof.

8. The method of claim **1**, wherein the pharmaceutical composition has a pH in the range of about 4.5 to about 5.5.

9. The method of claim **1**, wherein the pharmaceutical composition has a pH of about 4.8 to about 5.2.

10. The method of claim **1**, wherein the pharmaceutical composition is isotonic.

11. The method of claim **1**, wherein the pharmaceutical composition further comprises sodium chloride, citric acid and sodium citrate.

12. The method of claim **1**, wherein the pharmaceutical composition is sterile, isotonic and has a pH of about 4.8 to about 5.2.

13. The method of claim **1**, wherein the pharmaceutical composition is administered using a jet nebulizer.

14. The method of claim **1**, wherein the pharmaceutical composition is administered once daily.

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